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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/822,639	04/12/2004	Darryl J. C. Pappin	BP0309US-CP1	1937

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APPLIED BIOSYSTEMS
500 OLD CONNECTICUT PATH
FRAMINGHAM, MA 01701

EXAMINER	
CORDERO GARCIA, MARCELA M	
ART UNIT	**PAPER NUMBER**
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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/822,639	PAPPIN ET AL.	
	Examiner	Art Unit	
	Marcela M. Cordero Garcia	1654	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *02 July 2007*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *21-54* is/are pending in the application.

4a) Of the above claim(s) *42-50,53 and 54* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *21-41 and 51-52* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

This Office Action is in response to the reply received on July 2, 2007.

Any rejection from the previous office action, which is not restated here, is withdrawn.

Claims 21-54 are pending in the application. Claims 21-31 were previously examined. Newly submitted claims 42-50 and 53-54 are directed to an invention that is independent or distinct from the invention originally claimed for the following reasons: Claims 42-50 and 53 are drawn to a single fragment ion as opposed to the instantly elected mixtures of fragment ions, therefore they are drawn to a broader invention. Claim 54 is drawn to a collection of fragment ions but does not include the limitations instantly claimed (i.e., generated by fragmentation of at least two differentially labeled molecules of an analyte wherein at least 2 of the differentially labeled analyte molecules are compounds of a given formula) as in claim 21 and therefore is also drawn to a broader invention. Newly submitted claims 32-41 and 51-52 have been examined.

Since applicant has received an action on the merits for the originally presented invention, this invention has been constructively elected by original presentation for prosecution on the merits. Accordingly, claims 42-50 and 53-54 are withdrawn from consideration as being directed to a non-elected invention. See 37 CFR 1.142(b) and MPEP § 821.03.

Claims 21-41 and 51-52 are presented for examination in the merits.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 21-41 and 51-52 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. The MPEP states that the purpose of the written description requirement is to ensure that the inventor had possession, as of the filing date of the application, of the specific subject matter later claimed by him. The courts have stated:

> "To fulfill the written description requirement, a patent specification must describe an invention and do so in sufficient detail that one skilled in the art can clearly conclude that "the inventor invented the claimed invention." Lockwood v. American Airlines, Inc., 107F.3d 1565, 1572, 41 USPQ2d 1961, 1966 (1997); In re Gosteli, 872 F.2d 1008, 1012, 10 USPQ2d 1614, 1618 (Fed. Cir. 1989) (" [T]he description must clearly allow persons of ordinary skill in the art to recognize that [the inventor] invented what is claimed."). Thus, an applicant complies with the written description requirement "by describing the invention, with all its claimed limitations, not that which makes it obvious," and by using "such descriptive means as words, structures, figures, diagrams, formulas, etc., that set forth the claimed invention." Lockwood, 107 F.3d at 1572, 41 USPQ2d at 1966." Regents of the University of California v. Eli Lilly & Co., 43 USPQ2d 1398.

The MPEP lists factors that can be used to determine if sufficient evidence of possession has been furnished in the disclosure of the Application. These include "level

of skill and knowledge in the art, partial structure, physical and/or chemical properties, functional characteristics alone or coupled with a known or disclosed correlation between structure and function, and the method of making the claimed invention. Disclosure of any combination of such identifying characteristics that distinguish the claimed invention from other materials and would lead one of skill in the art to the conclusion that the applicant was in possession of the claimed species is sufficient." MPEP 2163.

Further, for a broad generic claim, the specification must provide adequate written description to identify the genus of the claim. In Regents of the University of California v. Eli Lilly & Co., the court stated:

> "A written description of an invention involving a chemical genus, like a description of a chemical species, 'requires a precise definition, such as by structure, formula, [or] chemical name,' of the claimed subject mattersufficient to distinguish it from other materials. Fiers, 984 F.2d at 1171, 25 USPQ2d at 1606; In re Smythe, 480 F.2d 1376, 1383, 178 USPQ 279, 284-85 (CCPA 1973) ("In other cases, particularly but not necessarily, chemical cases, where there is unpredictability in performance of certain species or subcombinations other than those specifically enumerated, one skilled in the art may be found not to have been placed in possession of a genus. . . ."). Regents of the University of California v. Eli Lilly & Co., 43 USPQ2d 1398.

The MPEP further states that if a biomolecule is described only by a functional characteristic, without any disclosed correlation between function and structure of the sequence, it is "not sufficient characteristic for written description purposes, even when accompanied by a method of obtaining the claimed sequence." MPEP 2163. The MPEP does state that for generic claim the genus can be adequately described if the disclosure presents a sufficient number of representative species that encompass the genus. MPEP 2163. If the genus has a substantial variance, the disclosure must describe a sufficient variety of species to reflect the variation within that genus. See

MPEP 2163. Although the MPEP does not define what constitute a sufficient number of representative, the Courts have indicated what do not constitute a representative number species to adequately describe a broad generic. In Gostelli, the Court determined that the disclosure of two chemical compounds within a subgenus did not describe that subgenus. In re Gostelli, 872 F.2d at 1012, 10 USPQ2d at 1618.

In the instant case, the claims are drawn to mixture of fragment ions existing in a mass spectrometer derived by fragmentation of at least two differentially labeled molecules of an analyte, wherein the analyte is, e.g., a peptide, a protein, a nucleic acid, a carbohydrate, lipid or steroid, a small molecule. In regards to the term "analyte", this is a very broad generic label, which can be associated with almost any compound. See disclosure, page 4, lines 8-25, which defines "analyte" as a molecule of interest which may be determined. Analytes include the instantly claimed peptides, proteins, nucleic acid, carbohydrate, lipid, steroid, or small molecules, which are not adequately described and/or represented in the examples. The claims are conjugated to N-methyl-piperazine acetic acids differentially labeled. A mere statement that such analytes would be desirable for conjugation does not sufficiently provide ample written description pages describing the full breadth of the conjugates and fragment ions thereof within a mass spectrometer as instantly claimed. Please note that the greatly diversity of uncountable analytes, and the piperazine conjugates thereof have very different chemistries, solubilities, molecular weights, ionization potentials, fragmentation pathways upon ionization, interference ions, and so forth. The specification does provide examples of what qualify as compounds of the claimed invention (see, e.g, disclosure, page 4), and, since it does not limit the term 'analyte', the invention is drawn to an exceedingly large number of species. However, the examples are limited to a few conjugates and their ions, such as a few peptidic conjugates. As stated earlier, the

MPEP states that written description for a genus can be achieved by a representative number of species within a broad generic. It is unquestionable claim 1 is a broad generic with respect all possible compounds encompassed by the claims. The possible structural variations are limitless to conjugates of the claimed piperazines with any molecule, either biomolecular, organic or inorganic. It must not be forgotten that the MPEP states that if a biomolecule is described only by a functional characteristic, without any disclosed correlation between function and structure of the sequence, it is "not sufficient characteristic for written description purposes, even when accompanied by a method of obtaining the claimed sequence." MPEP 2163. Here, though the claims may recite a conjugation limitation claims lack written description because there is no disclosure of a correlation between function and structure of the compounds beyond compounds disclosed in the examples in the specification. Moreover, the specification lack sufficient variety of species to reflect this variance in the genus since the specification does not provide a representative number examples of conjugates with e.g., phosphopeptides, carbohydrates, nucleic acids, enzymes, polymers, double stranded nucleic acid, small molecules of any type, peptides of any sequence or length, proteins of any conformation, sequence and length, and so forth. The description requirement of the patent statute requires a description of an invention, not an indication of a result that one might achieve if one made that invention. See In re Wilder, 736 F.2d 1516, 1521, 222 USPQ 369, 372-73 (Fed. Cir. 1984) (affirming rejection because the specification does "little more than outlin[e] goals appellants hope the claimed invention achieves and the problems the invention will hopefully ameliorate."). Accordingly, it is deemed that the specification fails to provide adequate written description for the genus of the claims and does not reasonably convey to one skilled in

the relevant art that the inventor(s), at the time the application was filed, had possession of the entire scope of the claimed invention.

Applicant's arguments

Applicant argues that there is a strong presumption that an adequate written description of the claimed invention is present when the application is filed " MPEP 2163(I)(A). The examiner, therefore, must have a reasonable basis to challenge the adequacy of the written description. MPEP 2163.04. In rejecting a claim, the examiner must set forth express findings of fact which support the lack of written description conclusion. In addition Applicant cites MPEP 2163: "Information which is well known in the art need not be described in detail in the specification".

In a nutshell, Applicant writes that the rejection argues that there is insufficient written description to support use of "analyte" in the claimed subject matter. Although presented as a rejection for lack of written description because Applicants allegedly lack "possession" of the broad term "analyte". Regrettably, this angst over breath of the claimed subject matter is misguided and prejudicial.

Applicant argues that the original claims were allowed using substantially same language. Accordingly, it is remarkable that this rejection is now presented for the first time. Regardless, by its reliance on quotations from "California v. Eli Lilly & Co., 43 USPQ2d 1398" and the statement: "It must not be forgotten that the MPEP states that if a biomolecule is described only by functional characteristics, without any disclosed correlation between function and structure of the sequences, it not sufficient characteristics for written description purposes, even when accompanied by a method

of obtaining the claimed sequence" (OA at page 5). It would seem that the Office considers the analyte to be that which has been invented.

A review of the claims reveals that it is not the nature of the analyte which bestows inventiveness to the claimed subject matter. Rather, it is the unique natures of the linked N-methyl-piperazine acetic acid moiety (or fragment ions derived therefrom in a mass spectrometer) which bestows inventiveness on the claimed subject matter. Thus, these arguments supporting the rejection are misguided. The rejection is also prejudicial since it precludes Applicants from generically claiming subject matter related to various types of analyte molecules of interest to the ordinary practitioner labeled with the unique N-methyl-piperazine acetic acid moieties developed. Since analytes are not being invented, any analyte molecule of interest, that can be labeled with the inventive labeling reagents comprising the N-methyl piperazine acetic acid (described herein), would be within the knowledge of one of skill in the art, and thus, need not be described in detail in the specification. MPEP 2163(II)(A)(2).

Moreover, Applicant demonstrates possession of the invention "... by describing the claimed invention with all of its limitations using such descriptive means as words, structures, figures, diagrams, and formulas that fully set forth the claimed invention. MPEP 2163(I). Analyte is defined, *inter alia*, in the specification at page 4 as: "a molecule of interest that may be determined". The specification further describes methods for labeling said analytes with the disclosed labeling reagents comprising the N-methyl piperazine acetic acid moiety and the analyzing fragment ions of said labeled analytes in a mass spectrometer. As noted in the Office Action at page 4, examples of

analytes expressly described in the specification include peptides, proteins, nucleic acids, carbohydrates, lipids, steroids and small molecules (with a molecular weight of less than 1500 Da.). Thus it is clear that the specification uses words, structures, figures, diagrams and formulas that fully set forth the claimed invention. From this standpoint compliance with the written description requirement is self-evident.

Response to Applicant's arguments

Applicant's arguments filed on July 2, 2007 have been fully considered but they are not persuasive for the reasons set forth above and because the invention does in fact inherently does comprise the instantly claimed analytes and piperazine labels which generate the analyte-identifying mixture of ions to be detected by mass spectrometric methods.

An adequate written description of a chemical invention also requires a precise definition, such as by structure, formula, chemical name, or physical properties, and not merely a wish or plan for obtaining the chemical invention claimed. See, e.g., Univ. of Rochester v. G.D. Searle & Co., 358 F.3d 916, 927, 69 USPQ2d 1886, 1894-95 (Fed. Cir. 2004) (The patent at issue claimed a method of selectively inhibiting PGHS-2 activity by administering a non-steroidal compound that selectively inhibits activity of the PGHS-2 gene product, however the patent did not disclose any compounds that can be used in the claimed methods. While there was a description of assays for screening compounds to identify those that inhibit the expression or activity of the PGHS-2 gene product, there was no disclosure of which peptides, polynucleotides, and small organic

molecules selectively inhibit PGHS-2. The court held that "[w]ithout such disclosure, the claimed methods cannot be said to have been described."). MPEP 2163 (II)(3)(a).

In addition MPEP 2163 (II)(3)(a)(ii) states:

> The written description requirement for a claimed genus may be satisfied through sufficient description of a representative number of species by actual reduction to practice (see i)(A), above), reduction to drawings (see i)(B), above), or by disclosure of relevant, identifying characteristics, i.e., structure or other physical and/or chemical properties, by functional characteristics coupled with a known or disclosed correlation between function and structure, or by a combination of such identifying characteristics, sufficient to show the applicant was in possession of the claimed genus (see i)(C), above). See Eli Lilly, 119 F.3d at 1568, 43 USPQ2d at 1406.

In the instant case, and upon reconsideration after request for continued examination after allowance, Examiner deems that the exemplified peptides in the disclosure do not adequately describe the genus, for example, proteins or nucleic acids with much larger molecular weights, or smaller molecules which may have competing ionization barriers at different bonds and therefore may not produce the expected indicative fragment ions. See also:

> A "representative number of species" means that the species which are adequately described are representative of the entire genus. Thus, when there is substantial variation within the genus, one must describe a sufficient variety of species to reflect the variation within the genus. The disclosure of only one species encompassed within a genus adequately describes a claim directed to that genus only if the disclosure "indicates that the patentee has invented species sufficient to constitute the gen[us]." See Enzo Biochem, 323 F.3d at 966, 63 USPQ2d at 1615; Noelle v. Lederman, 355 F.3d 1343, 1350, 69 USPQ2d 1508, 1514 (Fed. Cir. 2004) (Fed. Cir. 2004)("[A] patentee of a biotechnological invention cannot necessarily claim a genus after only describing a limited number of species because there may be unpredictability in the results obtained from species other than those specifically enumerated."). MPEP 2163 (II)(3)(a).

Accordingly, it is deemed that the specification fails to provide adequate written description for the genus of the claims and does not reasonably convey to one skilled in

the relevant art that the inventor(s), at the time the application was filed, had possession of the entire scope of the claimed invention.

Conclusion

No claim is allowed.

The prior art made of record and not relied upon is considered pertinent to applicant's disclosure.

THIS ACTION IS MADE FINAL. Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Marcela M. Cordero Garcia whose telephone number is (571) 272-2939. The examiner can normally be reached on M-Th 7:30-6:00.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Cecilia J. Tsang can be reached on (571) 272-0562. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

Marcela M Cordero Garcia
Patent Examiner
Art Unit 1654

MMCG 08/07

Cecilia J. Tsang
Supervisory Patent Examiner
Technology Center 1600